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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,263	WANG, XIAO B.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-19,23-33 and 44-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-19,23-33 and 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed May 29, 2007 is acknowledged. Claims 1, 5-19, 23-33, and 44-48 are currently pending. In the response, claims 1 and 47 were amended, and claims 2 and 4 were canceled. Applicant's opening remarks state that claim 48 was not addressed in the previous Office Action and request status of the claim (see page 10). Claim 48 was rejected under 35 U.S.C. 103(a) as unpatentable over Oliphant in view of Robertson (see page 11 of the Office Action mailed 12/28/2006). This Office Action is made non-final due to the inclusion of new grounds of rejection not necessitated by Applicant's amendment (see sections 3-5 below).

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 09/862,417 (now USPN 6,824,980) and Provisional Application 60/209,987, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more

claims of this application. Specifically, the prior-filed applications do not provide support for hybridizing the equal-length extension products generated in the first hybridization reaction with a second primer and conducting a second primer extension reaction. Therefore, the examined claims (1-33 and 44-48) have not been granted benefit of the earlier filing date of the above applications (09/862,417 & 60/209,987), and the instant application filing date of January 14, 2004 has been used as the effective filing date for prior art purposes.

Claim Rejections - 35 USC § 112 (Enablement)

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are directed to a method to assist in cancer diagnosis comprising detection of a primer extension product generated from an oncogene or variant thereof. The invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

Claim 47 is broadly drawn to a method for assisting in the diagnosis of any cancer in any host based on the detection of an unspecified primer extension product generated from any oncogene or variation thereof. Hosts encompassed by the method of claim 47 include humans, rats, monkeys, cats, dogs, mice, rats, bacteria, and insects. Cancers encompassed by the method of claim 47 include, for example, lung cancer, bladder cancer, breast cancer, leukemia, prostate cancer, colon cancer, pancreatic cancer, and skin cancer. Oncogenes encompassed by the method include wild-type receptor tyrosine kinases, p53, G-protein coupled receptors, serine-threonine kinases, and transcription factors (see claim 48) as well as any conceivable variant thereof (e.g. insertions, deletions, substitutions, translocations). The different cancers encompassed by the method inherently possess radically different etiologies and symptoms and in many cases have no relationship to each other whatsoever in the same organism, let alone

within the diverse group of organisms encompassed by the claims. Also, the different oncogenes and variants thereof are related to cancer in radically different ways exerting their influence via diverse and often unrelated biochemical pathways. Thus, the claims are extremely broad in scope, covering determination in any host of the presence of any cancer or a predisposition to any cancer based on the detection of an unspecified primer extension product generated from any oncogene or variant thereof.

Quantity of Experimentation

The quantity of experimentation in this area is immense since there is complete variability as to whether or not the observation of a particular primer extension product in a sample obtained from a subject is sufficient to indicate the presence of cancer or a predisposition to cancer. An enormous quantity of study and experimentation including trials with dozens of patients would be required to determine that even a single disease is associated with any differentially expressed or variant gene or primer extension product generated therefrom. This would be an inventive, unpredictable and difficult undertaking in itself, and the efficacy of any of the genes, as a diagnostic for any particular disease would need to be demonstrated in a variety of patients with a statistically significant result. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004) 96(6): 434-442; cited previously) notes that in studies of the association of mutations with specific diseases larger studies with 1500 participants have significantly more statistical power than smaller studies (see page 435).

Similarly, Wei et al. (BMC Genomics (2004) 5: 87-96; cited previously) teaches that the studies conducted using larger sample sizes with more replicates have much better statistical power and relevance compared to studies using small sample sizes with few replicates (see page 2, col. 1 and page 8). So, the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association for even one of genes (in differentially expressed or variant form) disclosed by Applicant. To cover all possible disclosed differentially expressed and variant genes, tens of thousands of patient samples would be necessary, and to cover any fraction of the range of cancers encompassed by the method, hundreds of thousands of separate patients and the associated analyses would be required. Furthermore, this large amount of experimentation would have to be repeated in each of the different hosts encompassed by the claims (e.g. humans, mice, dogs, cats, rabbits, etc). This is a very large amount of experimentation.

The unpredictability of the art and the state of the prior art

The art teaches that it is entirely unpredictable how differentially expressed and variant genes are associated with disease. For example, Listgarten et al. (Clinical Cancer Research (2004) 10: 2725-2737; cited previously) analyzed 98 single nucleotide polymorphisms (SNPs) distributed over 45 genes of potential relevance to breast cancer in 174 patients and compared the results with matched normal controls (see abstract). Listgarten concluded that "No single SNP site on its own could achieve more than 60% in predictive accuracy" (abstract) and encouraged detection of multiple SNPs to further improve accuracy (see abstract and also page

2735, last paragraph). Even with detection of multiple SNPs, though, Listgarten only report an increase in predictive accuracy to 69% (page 2726, col. 1). Finally, it is important to note that the studies of Listgarten were performed using patients whose breast cancer status was known. In other words, Listgarten demonstrated correlations between *some* SNPs (only 3 out of 98 tested) and a specific condition, breast cancer, but did not positively diagnose patients with unknown disease status or determine a predisposition to cancer based solely on the detection of variant polynucleotides.

Applicant's own work (Benoit et al. (2005) BioTechniques 38(4): 635-639; cited previously) also illustrates the gap between detection of a differentially expressed or variant polynucleotide and a positive diagnosis. Benoit presents a colorimetric primer extension method of mutation detection (see abstract). Benoit emphasizes that the detection of variant polynucleotides is useful to "detect early markers of disease or to *aid* in diagnosis (emphasis added)" (page 638, col. 1), but does not advocate cancer diagnosis or determination of a predisposition to cancer based solely on the detection of a variant polynucleotide. Furthermore, the teachings of Benoit further support the fact that not every variant is useful as a disease indicator. Benoit repeatedly suggests using the method to rapidly detect the best-studied (and likely the most reliable indicators) polynucleotide variants (page 638, for example).

Finally, the art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18; cited previously) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is

consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6): 434-442) who notes, "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives" (see abstract). Ioannidis (Nature genetics (2001) 29:306-309; cited previously) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example). Finally, Wei states, "Microarray experiments are often performed with a small number of biological replicates, resulting in low statistical power for detecting differentially expressed genes and concomitant high false positive rates (abstract)."

Therefore, the art suggests that the detection of differentially expressed and/or variant genes is not usually sufficient for positive disease diagnosis or determination of a predisposition to cancer, but rather must be combined with additional test results. The art also suggests that many reported associations between differentially expressed and/or variant polynucleotides may be incorrect, thereby providing support for the conclusion that it is entirely unpredictable whether a given differentially expressed or variant gene will function in a diagnostic capacity for a given disease. Finally, given the fact that each of the different hosts contemplated by the invention has a different physiology and genetic makeup, it is also highly unpredictable that the results from one host can be simply extrapolated to any other host.

Working Examples

The specification has one relevant working example. Example 3 (page 23) teaches determination of the expression level of the cancer-related genes p53 and B-raf using the method of the invention. Two specific primer extension products were detected in relation to a specific

disease (breast cancer). However, the RNA samples used in this example were isolated from human breast cancer tissue rather than an undiagnosed sample, and no indication is given, either in this example, or elsewhere in the specification that the method outlined in Example 3 can be used to positively diagnose cancer or indicate a predisposition to cancer in the absence of additional tests. Also, no indication is given in the example or elsewhere that the method is applicable to any other subject than humans.

Guidance in the Specification

The specification teaches generally that the expression level of oncogenes such as p53, growth factors, receptor tyrosine kinases, membrane-associated non-receptor tyrosine kinases, G-protein coupled receptors, membrane-associated G proteins, serine/threonine kinases, and nuclear DNA-binding/transcription factors may be used to diagnose cancer or identify a predisposition to cancer (pages 12-13). Pages 12-13 also teach specific cancers in which specific examples of the above oncogenes have been observed, but fail to teach that reliable and reproducible diagnosis or determination of a predisposition to cancer is possible based on the presence of these nucleic acid sequences. Also, the specification is unclear as to what nucleic acid sequence should be detected – the wild type or a variant form, and if a variant from is to be detected, which variant form.

Furthermore, the specification provides no guidance on methods or techniques to demonstrate an association between any specific disease and any specific mutation or gene. The specification even fails to provide any discussion or description of the scientific steps necessary

to provide evidence that would associate a particular gene or variant thereof with a specific disorder from the extensive list of different types diseases and conditions.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the association of any differentially expressed or variant polynucleotide and any form of cancer in any host, where there is no teaching in the specification or art that any specific gene or gene variant is sufficient for cancer diagnosis or determination of a predisposition to cancer, in concert with the teaching that many published association studies are simply wrong supports a finding of undue experimentation. The specification provides the ordinary practitioner with no written description or guidance that leads to a reliable method of associating any specific differentially expressed or variant gene with any cancer or pre-cancerous state. Furthermore, the specification does not provide guidance to overcome art-recognized problems in the association of mutations and differentially expressed genes with diseases as shown by Lucentini, Wacholder, and Wei, among others. Finally, the quantity of experimentation is immense. Thus, given the broad claims to the diagnosis or determination of a predisposition to any cancer based on the detection of any primer extension product generated from any oncogene in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of

any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, the inevitable conclusion is that it would require undue experimentation for one of skill in the art to perform the method of the claims as broadly written.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1996 (Fed. Cir. 1997)."

In the instant case, independent claim 47 recites that the target polynucleotide is "an oncogene or variation thereof involved in or related to cancer." The specification states that a variant polynucleotide may comprise any type of mutation including substitutions, insertions, deletions, and translocations (page 18). For even a single oncogene, this is a very large genus of molecules, and in the instant case, where any oncogene may be used, the genus is simply

enormous, comprising millions of molecules that inherently possess different structural and functional properties.

Regarding genus claims, the MPEP states, "For each claim drawn to a genus: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

"A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented invention of any species other than the one disclosed." In re Curtis, 354 F3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)"

Applicant discloses the nucleic acid sequence of approximately 35 oncogenes (pages 13-14). Applicant also discloses approximately ten mutations occurring in oncogenes that are related to cancer or cancer susceptibility (pages 13-14). However, Applicant does not describe the structural or functional properties of any other nucleic acid sequence included in the broad genus comprising any oncogene or any variant thereof. This description of only a small number of oncogenes and an even smaller number of variants when the claimed genus contains millions of members does not satisfy the requirement to disclose a representative number of species. As a result, it must be concluded that at the time of filing, Applicant did not have possession of the claimed invention.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-19, 23-33, and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (EP 1 162 278 A2; cited previously) in view of Oliphant et al. (US 2003/0108900 A1; cited previously).

Wang teaches a method of primer extension that produces equal length extension products (see abstract and paragraphs 15-16).

Regarding claim 1, Wang teaches a method for detecting or quantifying a known target polynucleotide having a known nucleotide sequence comprising:

(a) hybridizing a first primer to a specific region of the known target polynucleotide and extending the first primer using one to three of four types of non-terminator nucleotides selected from A, T or U, G, and C to produce equal length primer extension products, wherein the extended portion of the first primer consists one to three of four types of nucleotides (see paragraphs 15-16 and 44; see also Figure 1)

(b) detecting the extension products from the first primer (paragraphs 15-16 and 44).

Regarding claim 5, Wang teaches that the amount of detectable extension product correlates to the amount of target polynucleotide (paragraphs 15-16).

Regarding claim 6, Wang teaches annealing of the first primer under high stringency (paragraph 44).

Regarding claim 7, Wang teaches that the extension products from the first primer are detected using mass spectroscopy (paragraph 16) or fluorescence spectroscopy (paragraph 34).

Regarding claims 8 and 9, Wang teaches that the products from the first primer extension contain a detectable label (paragraphs 15, 16, and 44), such as a fluorophore, an eptiope, an enzyme, a polypeptide, a radioactive isotope, a dye, or biotin (paragraphs 11, 18 and 34).

Regarding claims 10 and 11, Wang teaches that the primer and target nucleic acid comprise DNA or RNA (paragraphs 15, 16, 20, and 25).

Regarding claims 12-14, Wang teaches enzymatic production of extension products using the template-dependent enzyme DNA polymerase, RNA polymerase, or reverse transcriptase (paragraphs 15, 28, and 44).

Regarding claims 15-19, Wang teaches in vitro enzymatic synthesis of the target nucleic acid by PCR (paragraph 20). Wang also teaches in vivo or non-enzymatic synthesis of the target nucleic acids (paragraph 19). Wang also teaches that the target nucleic acid may comprise genomic DNA, mRNA, or cDNA (paragraph 20). Wang further teaches that the target nucleic acid is obtained from a plant, microorganism, bacteria, virus, a vertebrate, or an invertebrate (paragraph 19).

Regarding claims 23-25, Wang teaches that the first primer comprises one or more moieties that permit affinity separation of the primer from unincorporated reagent and/or the polynucleotide of interest (see paragraph 27, where Wang teaches labeling the primer with biotin or digitonin).

Regarding claims 26 and 27, Wang teaches enzymatic, chemical or physical synthesis of the first primer on a solid support (paragraphs 25 and 27; see also claims 29-31).

Regarding claim 28, Wang teaches that the first primer is immobilized onto a solid support to produce an immobilized target nucleic acid sequence (paragraph 27).

Regarding claims 29 and 30, Wang teaches that the first primer can be cleaved from the solid support by a chemical process, specifically via cleavage of a photocleavable bond (see claims 33 and 37).

Regarding claim 31, Wang teaches that the solid support comprises beads, chips, capillaries, pins, combs, wafers, or flat surfaces (see claim 38).

Regarding claim 32, Wang teaches that the immobilization of the first primer is accomplished by hybridization between a complementary capture nucleic acid molecule, which has been previously immobilized to a solid support (see claim 39).

Regarding claim 33, Wang teaches that immobilization is accomplished via direct bonding between the solid support and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence (see claim 40).

Regarding claim 44, Wang teaches a method comprising:

(a) hybridizing a first primer to the target polynucleotide (paragraphs 15, 16, and 44)

(b) forming equal length primer extension products using one to three of four types of non-terminator nucleotides selected from A, T or U, G, and C to produce equal length primer extension products, wherein the extended portion of the first primer comprises one to three of four types of nucleotides (see paragraphs 15, 16, and 44)

(e) correlating the amount of detectable marker in the extension products of (b) with the amount of target polynucleotide (paragraphs 15, 16, and 44).

Wang does not teach hybridizing a second primer to the extended portion of the first primer and extending the second primer to form a second primer extension product.

Oliphant teaches primer extension-based methods of detecting nucleic acids.

Regarding claims 1 and 44, Oliphant teaches a method (see Figure 3) for detecting or quantifying a known target polynucleotide having a known nucleotide sequence comprising:

(a) hybridizing a first primer to a specific region of the known target polynucleotide and extending the first primer (see Figure 3, step 1 and 354)

(b) hybridizing the extended portion of the first primer to a second primer, wherein the second primer comprises a region for hybridizing only to the extended portion of the first primer (see Figure 3, step 3 and paragraph 354, where the second allele-specific primer is hybridized to

the extended product produced in step a; since the primers are target-specific, the second primer comprises a region for hybridizing only to the extended portion of the first primer)

(c) producing extension products from the second primer (Figure 3, step 3 and paragraph 354)

(d) detecting the extension products from the second primer (paragraph 354).

Regarding claims 5 and 44, in the method of Oliphant, the amount of detectable extension product correlates to the amount of target polynucleotide (paragraphs 354).

Regarding claim 6, Oliphant teaches annealing of the first and second primers under high stringency (paragraph 17).

Regarding claim 7, Oliphant teaches that the extension products from the second primer are detected using mass spectroscopy (paragraph 387) or fluorescence spectroscopy (paragraph 400).

Regarding claims 8 and 9, Oliphant teaches that the products from the second primer extension contain a detectable label (paragraph 354), such as a fluorophore, an eptiope, an enzyme, a polypeptide, a carbohydrate, a radioactive isotope, a dye, or biotin (paragraphs 96 and 337-341)

Regarding claims 10 and 11, Oliphant teaches that the primers and target nucleic acid comprise DNA or RNA (paragraphs 35 and 40).

Regarding claims 12-14, Oliphant teaches enzymatic production of extension products using the template-dependent enzyme DNA polymerase (see Figure 3 and paragraph 348).

Regarding claims 15-19, Oliphant teaches enzymatic synthesis of the target nucleic acid by PCR (paragraph 41). Oliphant also teaches that the target nucleic acid may comprise genomic

DNA, mRNA, or cDNA (paragraph 40). Oliphant further teaches that the target nucleic acid may be obtained from humans or mammals (which are vertebrates), bacteria or viruses (paragraph 31).

Regarding claims 23 and 25, Oliphant teaches that the first primer comprises one or more moieties that permit affinity separation of the primer from unincorporated reagent and/or the polynucleotide of interest (see Figure 3, where the first primer is biotinylated).

Regarding claims 24 and 25, Oliphant teaches that the second primer comprises one or more moieties that allow immobilization of the second primer onto a solid support to produce an immobilized second primer sequence (paragraph 354 teaches that the second primer is labeled; paragraphs 337-341 teach detectable labels include attachment moieties such as biotin).

Regarding claims 26 and 27, Oliphant teaches that the second primer is synthesized directly (via chemical synthesis) on a solid support to produce an immobilized second primer sequence (paragraph 337 teaches labeling with a nanocrystal – a solid support).

Regarding claim 28, Oliphant teaches that the first primer is immobilized onto a solid support to produce an immobilized target nucleic acid sequence (paragraph 354).

Regarding claims 29 and 30, Oliphant teaches that the first primer can be cleaved from the solid support by a chemical process, specifically via cleavage of a photocleavable bond (paragraphs 84 and 85 teach immobilization of primers on a solid support or array; paragraph 403 teaches photolithographic production of the array).

Regarding claim 31, Oliphant teaches that the solid support comprises beads or flat surfaces (paragraphs 84 & 85).

Regarding claim 32, Oliphant teaches that the immobilization of the first primer is accomplished by hybridization between a complementary capture nucleic acid molecule, which has been previously immobilized to a solid support (paragraphs 56-59).

Regarding claim 33, Oliphant teaches that immobilization is accomplished via direct bonding between the solid support and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence (paragraphs 87-90).

Regarding claim 45, the second primer of Oliphant hybridizes to the non-primer portion of the first extension product (see Figure 3, where the second primer hybridizes to the extended portion of the first primer extension product rather than the primer portion).

Regarding claim 46, a primer portion of the first extension product serves as a template for extending the second primer (see Figure 3).

Oliphant teaches that hybridization and extension of the second primer "provides allele discrimination and an additional level of locus specificity prior to signal amplification (see Figure 3)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Oliphant to the isometric primer extension method taught by Wang. An ordinary practitioner of the method taught by Wang would have been motivated to hybridize a second primer to the extended portion of the first primer and conduct primer extension since Oliphant taught that this second primer annealing and extension step provided an additional level of specificity control prior to signal amplification and detection (see Figure 3 and also paragraph 354). When applying the teachings of Oliphant to the method of Wang, an ordinary practitioner would have recognized that in order to obtain this specificity control, the

region of the second primer that hybridizes to the extended portion of the first primer must only contain the nucleotides utilized in the first primer extension. Since the method of Wang was designed to amplify nucleic acids having a known sequence (paragraphs 15, 16, and Figure 1), an ordinary practitioner would have had a reasonable expectation of success in designing and utilizing the second primer taught by Oliphant. Thus, the methods of claims 1, 5-19, 23-33, and 44-46 are prima facie obvious in view of the combined teachings of Wang and Oliphant.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 7-19, 23-33, and 44-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-10, 13-28, and 32-38 of U.S. Patent No. 6,824,980 in view of Oliphant et al. (US 2003/0108900 A1).

The instant claims are drawn to a method comprising primer extension with a mixture of up to three non-terminator nucleotides to produce a first primer extension product followed by a second round of primer extension using the first extension product as a template. The claims of the '980 patent recite identical or more specific limitations of the instant claims with the exception that the '980 patent does not recite a second primer extension step. Specifically, claims 1 and 36 of the '980 patent recite the limitations of the instant claims 1, 5, 7, and 44, again with the exception that the '980 patent does not recite a second primer extension step. The limitations of the instant claims 10-16 are recited in claims 2, 3, and 6-10 of the '980 patent. The limitations of the instant claims 17-19 are recited in claims 13-17 of the '980 patent. The limitations of the instant claims 23, 25, 28-33 are recited in claims 20-28, 32-34 and 38 of the '980 patent.

Oliphant teaches a primer extension method for analyzing nucleic acids as discussed in greater detail above (see Figure 3 and paragraph 354). Regarding claims 1 and 44, Oliphant teaches that annealing of a second primer to an extended region of the first primer "provides allele discrimination and an additional level of locus specificity prior to signal amplification (Figure 3)."

Regarding claim 24, Oliphant teaches that the second primer comprises one or more moieties that allow immobilization of the second primer onto a solid support to produce an immobilized second primer sequence (paragraph 354 teaches that the second primer is labeled; paragraphs 337-341 teach detectable labels include attachment moieties such as biotin).

Regarding claims 26 and 27, Oliphant teaches that the second primer is synthesized directly (via chemical synthesis) on a solid support to produce an immobilized second primer sequence (paragraph 337 teaches labeling with a nanocrystal – a solid support).

Regarding claim 45, the second primer of Oliphant hybridizes to the non-primer portion of the first extension product (see Figure 3, where the second primer hybridizes to the extended portion of the first primer extension product rather than the primer portion).

Regarding claim 46, a primer portion of the first extension product serves as a template for extending the second primer (see Figure 3).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to include a second primer extension step in the method recited in the '980 patent. An ordinary practitioner would have been motivated to do so, because Oliphant taught that this "provides allele discrimination and an additional level of locus specificity prior to signal amplification (Figure 3)." Therefore, the method of the instant claims is an obvious variant of the method recited in the claims of the '980 patent and the teachings of Oliphant.

Response to Arguments

7. Regarding the rejection of claims 1, 2, 4-19, 23-33 and 47 under 35 U.S.C. 102(a) and 102(e) as anticipated by Oliphant, Applicant's arguments, see pages 12-14, filed May 29, 2007 were fully considered and are persuasive. Oliphant does not teach all of the elements of amended claims 1 and 47, and therefore, the rejections have been withdrawn.

Regarding the rejection of claims 44-46 and 48 under 35 U.S.C. 103(a) as unpatentable over Oliphant in view of Wang, Applicant's arguments have been considered but are moot in view of the new grounds of rejection presented above.

Regarding the obviousness-type double patenting rejection citing US 6,824,980, Applicant states that a terminal disclaimer has been filed (see page 20). However, a terminal disclaimer could not be found in the application file. Therefore, the rejection has been maintained.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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